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| EXAMINER | |
|---|---|
| HUYNH, PHUONG N | |

| ART UNIT | PAPER NUMBER |
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| 1644 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| **Advisory Action Before the Filing of an Appeal Brief** | **Application No.** 10/580,108 | **Applicant(s)** QASBA ET AL. | |
|---|---|---|---|
| | **Examiner** PHUONG HUYNH | **Art Unit** 1644 | |

***--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

THE REPLY FILED 11 February 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *None* .
   Claim(s) objected to: *None*.
   Claim(s) rejected: *1,2,43-45 and 49*.
   Claim(s) withdrawn from consideration: *None*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☒ Other: See Continuation Sheet.

/Phuong Huynh/
Primary Examiner, Art Unit 1644

Continuation of 11. does NOT place the application in condition for allowance because:
The enablement and written description rejections of Claims 1-2, 43-45 and 49 stand rejected under 35 U.S.C. 112, first paragraph, for the reasons of record.

With respect to the enblement rejection, Applicants' arguments filed February 11, 2011 have been fully considered but are not found persuasive. Applicants' position is that the examiner has not submitted any evidence to doubt the disclosure is not enable for the claimed targeted glycoconjugate. Claims 1, 2, and 49 are directed to a glyconjugate which is not limited to a recited use. Applicants have exemplified that CREB or bovine lens alpha-crystallin can be labeled using recobinant O-Glc-NAc glycosylated CREB and the mutant Y289L O-GlcNAc glycosyltransferase and the generation. This level of enablemnt is at least acknowleged by the Examiner at pages 4-5 of the Office Action.

Contrary to applicants' assertion that the claimed glycoconjugate is not limited to a recited use, it is noted that claim 43 recites a pharmaceutical composition comprising the targeted glycoconjugate of claim 1. Claim 44 recites the intended use in a therapeutic method. Claim 45 recites the glycoconjugate for use in medical therapy. As such, the intended use of the unspecified glycoconjugate is for use as a pharmaceutical composition for treating any and all disease. Not only the binding specificity associated with the structure of such unspecified targeting compound such as glycoprotein, glycolipid or carbohydrate are not specified, there is insufficieng guidance as to the structure i.e., amino acid sequence of such "polypeptide" or nucleic acid sequence of such "nucleic acid" or "vaccine", "agonist", "antagonist", "cough and cold preparation" as bioactive agent. The specification does not teach how to predict which unspecified "polypeptide", "nucleic acid" is bioactive for use in which therapeutic method or treating which disease. Given the numerous unspecified glycoconjugate, there is insufficient in vivo working examples of using such unspecified glycoconjugate as a pharmaceutical composition or therapeutic methods. The specification provides no direction or guidance to assist one skilled in the art in producing the claimed glycoconjugate and for use in a pharmaceutical composition or for use in a therapeutic or diagnostic method or for use in medical therapy as defined by the claims. Given the lack of guidance as to the structure of polypeptide, nucleic acid, inhibitor, agonist and antagonist to any receptor, and the bindng specficitiy of the targeting compound, the lack of direction or in vivo working examples, the breadth of the claims, which encompass innumerable possible proteins, nucleic acid, chemical compound and targeting compound, and the amount of experimentation required to determine each possible species individually, it would require undue experimentation to use the invention in a manner commensurate in scope with the claims.

While the specification is enabled for a method of making a glycoconjugate using genetically engineered GalT transferase such as Y289L to modified UDP galataose acetyl gorup having a ketone group at the C2 position to join the targeting compound to the bioactive agent at said C2 position of the galactose ring, the claims are not drawn to a method of making a targeted glycoconjugate using genetically engineered GalT such as Y289L to modified UDP galataose acetyl gorup havign a kietone group at the C2 position to join the targeting compound to the bioactive agent at said C2 position. For method claims, applicants may claim a broader scope. However, for product claims, the scope of the glycoconjugate is limited to what is known (be able to make and use) about the targeting compound and the bioactive agent in the claimed glyconjugate. This is not reflected in claims 1 and 2. Furthermore, the claimed glycoconjugate does not have to be made by the genetically engineered GalT transferase such as Y289L as argued. For these reasons, the rejection is maintained.

With respect to the written description rejection, Applicants' arguments filed February 11, 2011 have been fully considered but are not found persuasive. Applicants' position is that the measurement of binding specificity and structural features of glycoconjugates are described and, if any experimentation would be required, such experimentation would be routine to one skilled in the art. Targeting compounds are described in the specification at page 10 and page 18. Applicants provide a particular example of antibodies as a targeting compound at p. 20 of the specification. Further, targeting compounds were well known in the art as described above. Moreover, binding specificity of glycoprotein, glycolipid or carbohydrate targeting compounds was known in the art at the time of filing. For example, antibodies were known in the art at the time of filing to be targeting compounds. In particular, monoclonal antibodies against tumor antigens were known in the art as cancer therapeutic agents at the time of filing. For example, clinical trials were conducted with various monoclonal antibody therapeutics, such as bevacizumab, a recombinant humanized anti-VEGF monoclonal antibody that has been evaluated in Phase II and Phase II trials, and Ramaswamy et al. (Clin Breast Cancer. 2003 Oct;4(4):292-4, provided herein) describe in combination with doclataxel in women with advanced breast cancer. Vande Putte et al. (Ann Rheum Dis. 2003 Dec;62(12): 1168-77, provided herein), evaluate the efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Carbohydrate based targeted therapeutics were also well known in the art. For example, insulin is a well known therapeutic. Poulsen et al. (Diabetes Care. 2003 Dec;26(12):3273-9, provided herein), test a combination therapy with insulin as part, rosiglitazone, and metformin to treat reduced insulin secretion and insulin resistance in skeletal muscle and liver in type 2 diabetes. Further, the anticancer compound doxombicin was well known by one of skill in the art at the time of filing as a targeted anticancer compound. Numerous publications from the time of filing teach the use of doxorubicin in clinical trials (see, e.g. Anton et al., Clin Breast Cancer. 2003 Oct;4(4):286-91, provided herein). Bioactive agents are described at pages 10 - 18. Further, bioactive agents were well known in the art. Further, it was known in the art at the time of filing that bioactive agents, such as those claimed, could be used to treat various diseases. For example, the Campbell et al. reference (Cancer Res September 1, 2006 66; 8707), provided herein, demonstrates that statins prevent breast cancer growth in vivo and in vitro. The Cascone et al. reference (Ann Oncol. 2006 Mar; 17 Suppl 2:ii46-48), provided herein, summarizes the clinical evidence on the anticancer activity of small molecule EGFR inhibitors in small cell lung cancer. Restivo et al. (Diabetes Care. 2006 Dec;29(12):2650-3), provided herein, teach botulinum toxin treatment for oropharyngeal dysphagia associated with diabetic neuropathy. Brennan et al. (N Engl J Med. 2006 Nov 9;355(19): 1967-77), abstract provided herein, compare a rabbit antithymocyte polyclonal antibody or basiliximab, an interleukin-2 receptor monoclonal antibody, in renal transplantation graft rejection. Villa et al. (Br J Cancer. 2006 Dec 4;95(11): 1459-66. Epub 2006 Nov 21), provided herein, show that a prophylactic quadrivalent HPV vaccine was effective through 5 years for prevention of persistent

infection and disease caused by HPV 6/11/16/18. Applicants have demonstrated that antibodies can be galactosylated with Y289L GalT having a chemical handle at the C2 position in Bioconjugate Chem. 2009, 20, 1228 - 1236 (provided herein). Applicants describe the utility of Y289L GalT to transfer a sugar residue with C2-keto-Gal (or GalNAz) from their UDP derivatives to the N-acetylglucosamine residue of glycoproteins or glycopeptides. (see, e.g. Figure 5 on page 1233). Moreover, Applicants teach that the conjugation technology is a viable method that can be used for detection and targeting therapies. (see, p. 1229). In Bioconjugate Chem. 1009, 20, 1383- 1389 (provided herein), Applicants describe the biological activity of the described glycoconjugates. For example, Applicants describe C-terminal extended fusion polypeptides of recombinant scFv fusion proteins that are used as the acceptor substrate for human polypeptide-alpha-N-acetylgalactosaminyltransferase II that transfers either GalNAc or 2-keto-Gal from their respective UDP-sugars to the side-chain hydroxyl group of the Thr residue(s). The fusion scFv proteins with the modified galactose are then conjugated with a fluorescence probe, Alexa488, that carries an orthogonal reactive group. The fluorescence labeled scFv proteins bind specifically to a human breast cancer cell line (SK-BR-3) that overexpresses the HER2 receptor, indicating that the in vitro folded scFv fusion proteins are biologically active and the presence of conjugated multiple Alexa488 probes in their C-terminal end does not interfere with their binding to the antigen.

In response, none of the rejected claims are drawn to any of the specified antibody listed above as targeting agent and the known bioactive agents listed above for the claimed glyconjugate as argued.

The claims are drawn to any glyconjugate comprising any bioactive agent such as any polypeptide, any nucleic acid, any vaccine, any agnist, any antagonist and any targeting compound such as any glycoprotein, any glycolipid, or any carbohydrate joined by a modified UDP galactose acetyl group comprising a ketone group attached to the C2 protein of the galactose ring as the linker.

The structure-function correlation set forth in the disclosure does not clearly allow persons of ordinary skill in the art to recognize that the applicant has in fact invented what is claimed because the disclosure only sets forth adequate written description for the known antibody and bioagent agent joined by a modified UDP-GalNAc having a ketone group attached to the C2 position of the galacose ring using a modified galactosylase with Y289L GalT having a chemical handle at the C2 position in the glycoconjugate.

The written description of the instant application does not reasonably convey to one skilled in the art that applicant was in possession of (i) any polypeptide, any nucleic acid, any vaccine, etc as bioactive agent in claim 2 and (2) any targeting compound is any glycoprotein, any glycolipid or any carbohydrate for the claimed glycoconjugate as a pharmaceutical composition because the disclosure does not allow one of skill in the art to visualize or recognize the structure of such "polypeptide" or "nucleic acid" or "vaccine" as bioactive agent and structure associated with binding specificity of any glycoprotein, glycolipid or carbohydrate required to practice the claimed invention. The specification does not disclose any relevant identifying characteristic for such polypeptide, nucleic acid, vaccine having what bioactivity and taregting agent to convey to one of skill in the art that fall within the boundaries of the asserted claim pharmaceutical composition comprising such. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed.” (see page 1117). The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (see Vas-Cath at page 1116). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF’s were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. For these reasons, the rejection is maintained.

Continuation of 13. Other: For the record, applicants stated at page 4 of the amendment filed February 11, 2011 tah tclaims 1-10, 43-43 and 49 are pending. Claims 1-3, 43-45 and 49 were rejected under 35 U.S.C. 112 first paragraph for enablement and written description rejections. Inspection of the record indicates that claim 3 has been canceled. Therefore, only claims 1-2, 43-45 and 49 are pending.